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(71) Applicant *(for all designated States except US)*: **EPIGENOMICS AG** [DE/DE]; Kastanienalle 24, D-10435 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LOFTON-DAY, Cathy** [US/US]; 23908 35th Avenue W., Brier, WA 98036 (US). **MODEL, Fabian** [US/US]; 734 Broadway Avenue E., Apt. 306, Seattle, WA 98102 (US). **SLEDZIEWSKI, Andrew** [US/US]; 17736 15th Avenue NW, Shoreline, WA 98177 (US). **RUJAN, Tamas** [DE/DE]; Venetastr. 7, D-13189 Berlin (DE). **LEWIN, Jörn** [DE/DE]; Lützowufer 24, D-10787 Berlin (DE). **DISTLER, Juergen** [DE/DE]; Hewaldstr. 2, D-10825 Berlin (DE).

(74) Agents: **DAVISON, Barry, L.** et al.; 2600 Century Square, 1501 Fourth Avenue, Seattle, WA 98101-1688 (US).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND NUCLEIC ACIDS FOR ANALYSES OF COLORECTAL CELL PROLIFERATIVE DISORDERS

(57) Abstract: The invention provides methods, nucleic acids and kits for detecting, or for detecting and distinguishing between or among colorectal cell proliferative disorders. The invention discloses genomic sequences the methylation patterns of which have utility for the improved detection of and differentiation between said class of disorders, thereby enabling the improved diagnosis and treatment of patients.

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INTERNATIONAL SEARCH REPORT

Inte al Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, Sequence Search, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] 15 May 2003 (2003-05-15), "Homo sapiens SLIT and NTRK-like family, member 1, mRNA (cDNA clone MGC:51091 IMAGE:4816570), complete cds." XP002328022 retrieved from EBI accession no. EM_HUM:BC051738 Database accession no. BC051738 abstract ----- -/--	46-50

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the international search report
13 May 2005	23. 08. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bradbrook, D

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/US2004/020336

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] 17 September 2001 (2001-09-17), "Homo sapiens mRNA for KIAA1910 protein, partial cds." XP002328023 retrieved from EBI accession no. EM_HUM:AB067497 Database accession no. AB067497 abstract	46-50

X	WO 02/24056 A (MARKOWITZ SANFORD ; UNIV CASE WESTERN RESERVE (US); GRADY WILLIAM (US)) 28 March 2002 (2002-03-28)	1,51
A	the whole document	2-8, 10-19, 21-44

X	WO 03/014388 A (TAUBERT HEIKE ; DISTLER JUERGEN (DE); EPIGENOMICS AG (DE); MODEL FABIA) 20 February 2003 (2003-02-20)	1,51
A	page 8, line 32 - page 20, line 31 page 23, line 1 - page 24, line 8; claims 1-40; table 1	2-8, 10-19, 21-44

X	TOYOTA M ET AL: "CpG island methylator phenotype in colorectal cancer" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 96, July 1999 (1999-07), pages 8681-8686, XP002307651 ISSN: 0027-8424	1,51
A	the whole document	2-8, 10-19, 21-44

X	VAN RIJNSOEVER M ET AL: "Characterisation of colorectal cancers showing hypermethylation at multiple CpG islands." GUT, vol. 51, no. 6, December 2002 (2002-12), pages 797-802, XP002328020 ISSN: 0017-5749	1,51
A	the whole document	2-8, 10-19, 21-44

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INTERNATIONAL SEARCH REPORT

Inter ial Application No
PC1/uS2004/020336

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RASHID ASIF ET AL: "CpG island methylation in colorectal adenomas" AMERICAN JOURNAL OF PATHOLOGY, vol. 159, no. 3, September 2001 (2001-09), pages 1129-1135, XP002328021 ISSN: 0002-9440	1,51
A	the whole document	2-8, 10-19, 21-44

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INTERNATIONAL SEARCH REPORT

ıtional application No.
PCT/US2004/020336

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 44,51
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 44 and 51 encompass a surgical method carried out on the human or animal body, the search has been carried out as if such a step were not included.

2. [X] Claims Nos.: 9,20,45
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-51 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 44,51

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery (claims 44,51)

Continuation of Box II.2

Claims Nos.: 9,20,45

Claim 9 refers to the use of at least two of the given genes as markers. Said claim is unclear and inconcise (Art.6 PCT) in that it encompasses a huge number of embodiments (the different choices of any two from the total in the group) such that a meaningful search is impossible. As the description appears to provide no specific embodiments in which SEQ ID NO.1 has been used in combination with other genes, no search was carried out for claim 9.

In claim 20, the sequences to be analysed are not defined, and it is not immediately apparent which sequences are intended. Therefore, said claim is unclear (Art.6 PCT) and cannot be searched.

Claim 45 is unclear (Art.6 PCT) to the extent that no meaningful search is possible across the entire scope of the claim. Said claim relates to a nucleic acid molecule that is not defined in terms of its technical features, but only with respect to a vaguely defined chemical treatment. Furthermore the term "derived from" is vague and open to interpretation. The only sequences derived from SEQ ID NO.1 that are clear from the application are those defined by SEQ ID Nos 304, 305, 420 and 421, these being possible results of a bisulfite treatment. However, as such subject-matter has been searched in respect of other claims (e.g. claim 46), no search is provided for claim 45.

It should be noted that claims 27, 32, 38, 43 and 43b refer to a large number of sequences to be used in the claimed method; said claims have been searched only with respect to the method as such. The sequences per se have not been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-51 (all partially)

A nucleic acid comprising at least 9 or 16 contiguous nucleotides of a "treated" DNA sequence consisting of SEQ ID No.304, 305, 420 or 421 or sequences complementary thereto; a method for detecting and/or detecting and distinguishing between or among colorectal cell proliferative disorders comprising contacting genomic DNA with (a) reagent(s) that distinguish methylated and non-methylated CpG dinucleotides within at least one or at least two target region(s) of the genomic DNA that comprises at least one CpG dinucleotide sequence, in particular wherein said at least one target region comprises or hybridizes to at least 16 contiguous nucleotides of the sequence defined by SEQ ID NO.1; a method for detecting and/or detecting and distinguishing between or among colorectal cell proliferative disorders comprising determining the expression levels at least of the gene defined by SEQ ID NO.1; a method for detecting and/or detecting and distinguishing between or among colorectal cell proliferative disorders comprising the ability of a methylation-sensitive restriction enzyme to cleave a target genomic DNA, wherein said target nucleic acid comprises or hybridizes to at least 16 contiguous nucleotides of the sequence defined by SEQ ID NO.1.

Invention 2: Claims 1-51 (all partially)

A nucleic acid comprising at least 9 or 16 contiguous nucleotides of a "treated" DNA sequence consisting of SEQ ID No.306, 307, 422 or 423 or sequences complementary thereto; a method for detecting and/or detecting and distinguishing between or among colorectal cell proliferative disorders comprising contacting genomic DNA with (a) reagent(s) that distinguish methylated and non-methylated CpG dinucleotides within at least one or at least two target region(s) of the genomic DNA that comprises at least one CpG dinucleotide sequence, wherein said at least one target region comprises or hybridizes to at least 16 contiguous nucleotides of the sequence defined by SEQ ID NO.2; a method for detecting and/or detecting and distinguishing between or among colorectal cell proliferative disorders comprising determining the expression levels at least of the gene defined by SEQ ID NO.2; a method for detecting and/or detecting and distinguishing between or among colorectal cell proliferative disorders comprising the ability of a methylation-sensitive restriction enzyme to cleave a target genomic DNA, wherein said target nucleic acid comprises or hybridizes to at least 16 contiguous nucleotides of the sequence defined by SEQ ID NO.2.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Inventions 3-64: Claims: 1-51 (all partially)

As invention 2, for genomic sequences 3-64 and their corresponding "treated" sequences.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PC1/US2004/020336

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		WO	0224056 A2	28-03-2002
		US	2005153351 A1	14-07-2005
		US	2003068620 A1	10-04-2003
WO 03014388 A	20-02-2003	DE	10139283 A1	13-03-2003
		CA	2455161 A1	20-02-2003
		WO	03014388 A2	20-02-2003
		EP	1421220 A2	26-05-2004
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